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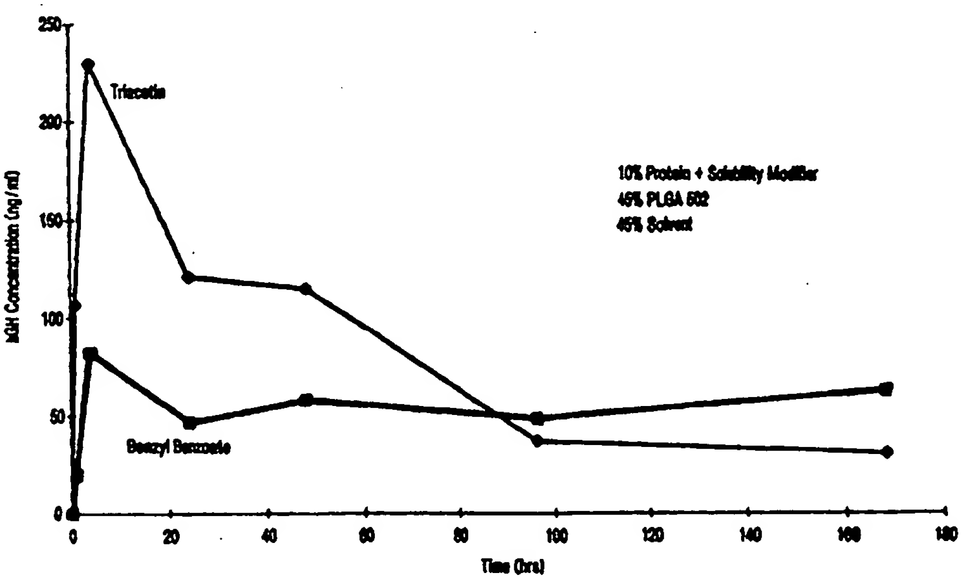

(57) Abstract

Methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject are described, and include, for example, compositions having burst indices of 8 or less for systemic applications and systems releasing 10 % or less of the total dose of beneficial agent in the first 24 hours after implantation for local applications. The compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent.

GEL COMPOSITION AND METHODS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a gel composition that can be implanted into a desired location and which can provide controlled release of a beneficial agent. The present invention also relates to methods of controlling release of a beneficial agent from a composition.

Description of the Related Art

Biodegradable polymers have been used for many years in medical applications. Illustrative devices composed of the biodegradable polymers include sutures, surgical clips, staples, implants, and sustained release drug delivery systems. The majority of these biodegradable polymers have been based upon glycolide, lactide, caprolactone, and copolymers thereof.

The biodegradable polymers can be thermoplastic materials which means that they can be heated and formed into various shapes such as fibers, clips, staples, pins, films, etc. Alternatively, they can be thermosetting materials formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures.

Although thermoplastic and thermosetting biodegradable polymers have many useful biomedical applications, there are several important limitations to their use in the bodies of various animals including humans, animals, birds, fish, and reptiles. Because these polymers generally are

Other illustrative osmotic delivery systems include those disclosed in U.S. Patent Nos. 3,797,492, 3,987,790, 4,008,719, 4,865,845, 5,057,318, 5,059,423, 5,112,614, 5,137,727, 5,151,093, 5,234,692, 5,234,693, 5,279,608, and 5,336,057. Pulsatile delivery devices are also known which deliver a beneficial agent in a pulsatile manner as disclosed in U.S. Patent Nos. 5,209,746, 5,308,348, and 5,456,679.

One way to avoid the incision needed to implant drug delivery systems is to inject them as small particles, microspheres, or microcapsules. For example, U.S. Patent No. 5,019,400 describes the preparation of controlled release microspheres via a very low temperature casting process. These materials may or may not contain a drug which can be released into the body. Although these materials can be injected into the body with a syringe, they do not always satisfy the demand for a biodegradable implant. Because they are particulate in nature, they do not form a continuous film or solid implant with the structural integrity needed for certain prostheses. When inserted into certain body cavities such as a mouth, a periodontal pocket, the eye, or the vagina where there is considerable fluid flow, these small particles, microspheres, or microcapsules are poorly retained because of their small size and discontinuous nature. Further, the particles tend to aggregate and thus their behavior is hard to predict. In addition, microspheres or microcapsules prepared from these polymers and containing drugs for release into the body are sometimes difficult to produce on a large scale, and their storage and injection characteristics present problems. Furthermore, one other major limitation of the microcapsule or small-particle system is their

is described as being effective to provide about at least 10% solubility in water. The polymer matrix systems are described as forming a porous core surrounded by a porous skin.

U.S. Patent No. 5,242,910 describes a sustained release composition containing drugs for treating periodontal disease. The composition comprises copolymers of lactide and glycolide, triacetin (as a solvent/plasticizer) and an agent providing relief of oral cavity diseases. The composition can take the form of a gel and can be inserted into a periodontal cavity via a syringe using either a needle or a catheter. As additional optional components, the composition can contain surfactants, flavoring agents, viscosity controlling agents, complexing agents, antioxidants, other polymers, gums, waxes/oils, and coloring agents. One illustrative viscosity controlling agent set forth in one of the examples is polyethylene glycol 400.

U.S. Patent No. 5,620,700 describes a polymer-drug matrix, optionally including plasticizers in an amount up to about 30 wt %, for local application of drug in the peridontal cavity. Among the plasticizers listed are, *inter alia*, triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate, diethyl phthalate, diethyl tartrate, ethyl lactate, triacetin and diacetin. The polymer matrix is non-flowable prior to administration and is heated to become flowable so that it may be dispensed into the peridontal cavity where it solidifies. While the patent discusses possible systemic applications by delivery via the ocular sacs of the eye or intravaginal delivery, it does not address the issue of burst of drug or methods of controlling burst.

agent can result in adverse consequences to the subject being treated, or where it is necessary to mimic the naturally-occurring daily profile of beneficial agents, such as hormones and the like, in the body of the subject being treated.

In an attempt to control burst and modulate and stabilize the delivery of the beneficial agent the prior art has coated particles of beneficial agent to retard release into an aqueous environment and extend release of the beneficial agent over time. Alternatively, various stabilizing or release modulating agents, such as metal salts as described in U.S. Patents 5,656,297; 5,654,010; 4,985,404 and 4,853,218 have been used. Notwithstanding some success, those methods have not been entirely satisfactory for the large number of beneficial agents that would be effectively delivered by implants, since in many instances the modulation and stabilization effect is the result of the formation of a complex of the metal ion with the beneficial agent. When such complexes do not form, the stabilization/modulation effect may not be adequate to prevent undesirable "burst" of the beneficial agent upon its introduction into the implant site.

Additionally, with conventional low viscosity, solvent-based depot compositions comprised of a polymer dissolved in a solvent, another problem which often exists is that the composition solidifies slowly after injection as solvent diffuses from the depot and water migrates into the depot. Since these compositions are relatively non-viscous in order to be injected, a large percentag of drug may be rapidly released as the system forms by diffusion of the solvent, particularly when the beneficial agent is soluble in the solvent

presenting a controlled, sustained release of beneficial agent to the subject being treated. What one observes, then, is a burst of beneficial agent being released in a short time period immediately after implantation, a lag time in which no or very little beneficial agent is being released, and subsequently continued delivery of beneficial agent (assuming beneficial agent remains after the burst) until the supply of beneficial agent is exhausted.

SUMMARY OF THE INVENTION

The present invention provides a method and an implantable system for systemic and local delivery of a beneficial agent to a subject. The method and system provide controlled release of beneficial agent to the subject being treated and limit the initial burst of beneficial agent from the implant system. Additionally, the invention provides a method of preparing implant systems having restricted initial burst of beneficial agent.

In one aspect, the invention comprises a method of administering, locally or systemically, a beneficial agent to a subject which comprises implanting a system comprising a beneficial agent dispersed or dissolved substantially throughout a viscous gel, the system releasing 20% or less by weight of the beneficial agent present in the viscous gel within the first 24 hours after implantation in the subject. Preferably, 10% or less by weight of the beneficial agent will be released within the first 24 hours after implantation.

In another aspect, the invention comprises a method of systemically administering a beneficial agent to a subject which comprises implanting a

having a miscibility in water of less than 7% by weight. Preferably, the miscibility in water of the solvent mixture is 20% or less by weight, and more preferably 10% or less by weight.

In yet another aspect, the invention comprises an implantable, biodegradable composition for delivery of a beneficial agent to a subject wherein the composition comprises a polymer; an effective plasticizing amount of a solvent to form a viscous gel with the polymer; and a beneficial agent dissolved or dispersed in the gel, wherein the solvent comprises a single solvent or a mixture of solvents with at least one solvent having a miscibility in water of less than 7% by weight selected from lower alkyl and aralkyl esters of benzoic acid.

In another aspect the present invention provides an implantable gel composition for systemic delivery of a beneficial agent to a subject comprising:

A) a biocompatible polymer;

B) a biocompatible solvent, having miscibility in water of less than 7% by weight and capable of dissolving the polymer and forming a viscous gel, said solvent being selected from the group comprising compounds having the following structural formula:

$$R_1 - \overset{\displaystyle O}{C} - O - R_2$$

In a further aspect, the present invention provides a method of restricting uptake of wafer by a gel composition which comprises forming the gel composition from a polymer and a solvent that forms a viscous gel with the polymer, the solvent having a miscibility in water of less than 7% by weight. Preferably, the solvent will have a miscibility in water of 6% or less by weight, and more preferably 5% or less by weight.

In another aspect, the present invention provides a method of preparing an injectable gel composition comprising:

A) mixing a biocompatible polymer and a solvent having a miscibility in water of 7% or less selected from lower alkyl and aralkyl esters of benzoic acid to form a viscous gel;

B) dispersing or dissolving a beneficial agent, optionally associated with a solubility modulator of the beneficial agent, in an emulsifying agent to form a beneficial agent containing emulsifying agent; and

C) mixing the beneficial agent containing emulsifying agent with the viscous gel, said beneficial agent containing emulsifying agent forming a dispersed droplet phase in the viscous gel, and optionally,

D) mixing one or more of a pore former and an osmotic agent with said viscous gel.

In another aspect, the present invention provides a method of preparing an implantable gel composition comprising:

A) mixing a biocompatible polymer and a solvent having a miscibility in water of 7% or less selected from lower alkyl and aralkyl esters of benzoic acid to form a viscous gel;

C) a beneficial agent; and optionally, one or more of the following:

D) an emulsifying agent;

E) a pore former;

F) a solubility modulator of the beneficial agent, optionally associated with the beneficial agent; and

G) an osmotic agent;

wherein at least the beneficial agent, optionally associated with the solubility modulator, is maintained separated from the solvent until the time of administration of the beneficial agent to a subject.

In still another aspect, the invention comprises an implantable composition for the systemic delivery of a beneficial agent comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a solvent to form a viscous gel with the polymer; and a beneficial agent selected from the group consisting of cDNA, DNA, peptides, proteins and fragments and derivatives thereof, said composition having a burst index of 8 or less.

In another aspect, the invention comprises an implantable composition for the sustained delivery of a beneficial agent comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a solvent selected from lower alkyl and aralkyl esters of benzoic acid to form a viscous gel with the polymer; and a beneficial agent.

In a further aspect, the invention comprises an implantable composition comprising a viscous gel and a beneficial agent dispersed or

Figure 3 is a graph illustrating the viscosity profiles of emulsions at different shear rates of water alone and of an aqueous mixture of ethanol, and of the viscous gel without emulsifying agent;

Figures 4A and 4B are graphs illustrating the degree of water uptake for various polymer-solvent mixtures, some of which form a part of this invention, and demonstrating that as the miscibility of the solvent in water decreases, the amount of water taken up into the implant decreases; and

Figures 5A and 5B are graphs of *in vivo* release rate profiles of non-stabilized and zinc-stabilized human growth hormone from gels formed from PLGA and the solvents triacetin and benzyl benzoate, respectively.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method of systemically or locally administering a beneficial agent to a subject by implanting in the subject an implantable system, formed as a viscous gel from a biocompatible polymer and a biocompatible solvent, and a beneficial agent is substantially dissolved or dispersed throughout the gel. By appropriate choice of solvent, water migration from the aqueous environment surrounding the implant system is restricted, and beneficial agent is released to the subject over a prolonged period of time, thus providing for delivery of the beneficial agent with a controlled burst of beneficial agent and sustained release thereafter.

It has been discovered that when a solvent having a solubility in water of less than 7% by weight in water is present in the system, suitable burst control and sustained delivery of beneficial agent is achieved, whether or not a solubility modulator of the beneficial agent is present in the system.

pharmaceutical excipients and other additives that do not change the beneficial aspects of the present invention. The addition of a solubility modulator to the implant system may enable the use of a solvent having a solubility of 7% or greater in the implant system with minimal burst and sustained delivery under particular circumstances. However, it is presently preferred that the implant system utilize at least one solvent having a solubility in water of less than 7% by weight, whether the solvent is present alone or as part of a solvent mixture. It has also been discovered that when mixtures of solvents which include a solvent having 7% or less by weight solubility in water and one or more miscible solvents, optionally having greater solubility, are used, implant systems exhibiting limited water uptake and minimal burst and sustained delivery characteristics are obtained.

Definitions

The term "beneficial agent" means an agent that effects a desired beneficial, often pharmacological, effect upon administration to a human or an animal, whether alone or in combination with other pharmaceutical excipients or inert ingredients.

The term "AUC" means the area under the curve obtained from an *in vivo* assay in a subject by plotting blood plasma concentration of the beneficial agent in the subject against time, as measured from the time of implantation of the composition, to a time "*t*" after implantation. The time *t* will correspond to the delivery period of beneficial agent to a subject.

The term "burst index" means, with respect to a particular composition intended for systemic delivery of a beneficial agent, the quotient formed by

that is to be delivered from an implanted composition. It is understood that the initial burst may vary depending on the shape and surface area of the implant. Accordingly, the percentages and burst indices associated with initial burst described herein are intended to apply to compositions tested in a form resulting from dispensing of the composition from a standard syringe.

The term "solubility modulator" means, with respect to the beneficial agent, an agent that will alter the solubility of the beneficial agent, with reference to polymer solvent or water, from the solubility of beneficial agent in the absence of the modulator. The modulator may enhance or retard the solubility of the beneficial agent in the solvent or water. However, in the case of beneficial agents that are highly water soluble, the solubility modulator will generally be an agent that will retard the solubility of the beneficial agent in water. The effects of solubility modulators of the beneficial agent may result from intereactions of the solubility modulator with the solvent, or with the beneficial agent itself, such as by the formation of complexes, or with both. For the purposes hereof, when the solubility modulator is "associated" with the beneficial agent, all such interactions or formations as may occur are intended. Solubility modulators may be mixed with the beneficial agent prior to its combination with the viscous gel or may be added to the viscous gel prior to the addition of the beneficial agent, as appropriate.

The term "subject" means, with respect to the administration of a composition of the invention, an animal or a human being.

Since all solvents, at least on a molecular level, will be soluble in water (i.e., miscible with water) to some very limited extent, the term "immiscible" as

polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and mixtures thereof.

Presently preferred polymers are polylactides, that is, a lactic acid-based polymer that can be based solely on lactic acid or can be a copolymer based on lactic acid and glycolic acid which may include small amounts of other comonomers that do not substantially affect the advantageous results which can be achieved in accordance with the present invention. As used herein, the term "lactic acid" includes the isomers L-lactic acid, D-lactic acid, DL-lactic acid and lactide while the term "glycolic acid" includes glycolide. Most preferred are poly(lactide-co-glycolide)copolymers, commonly referred to as PLGA. The polymer may have a monomer ratio of lactic acid/glycolic acid of from about 100:0 to about 15:85, preferably from about 60:40 to about 75:25 and an especially useful copolymer has a monomer ratio of lactic acid/glycolic acid of about 50:50.

The lactic acid-based polymer has a number average molecular weight of from about 1,000 to about 120,000, preferably from about 5,000 to about 30,000 as determined by gas phase chromatography. As indicated in aforementioned U.S. Patent No. 5,242,910, the polymer can be prepared in accordance with the teachings of U.S. Patent No. 4,443,340. Alternatively, the lactic acid-based polymer can be prepared directly from lactic acid or a mixture of lactic acid and glycolic acid (with or without a further comonomer) in accordance with the techniques set forth in U.S. Patent No. 5,310,865. The contents of all of these patents are incorporated by reference. Suitable lactic acid-based polymers are available commercially. For instance, 50:50

20°C, and weighed, and a candidate solvent is added dropwise. The solution is swirled to observe phase separation. When the saturation point appears to be reached, as determined by observation of phase separation, the solution is allowed to stand overnight and is re-checked the following day. If the solution is still saturated, as determined by observation of phase separation, then the percent (w/w) of solvent added is determined. Otherwise more solvent is added and the process repeated. Solubility or miscibility is determined by dividing the total weight of solvent added by the final weight of the solvent/water mixture. When solvent mixtures are used, for example 20% triacetin and 80% benzyl benzoate, they are pre-mixed prior to adding to the water.

Solvents useful in this invention are generally less than 7% water soluble by weight as described above. Solvents having the above solubility parameter may be selected from the lower alkyl and aralkyl esters of aryl acids such as benzoic acid, the phthalic acids, salicylic acid, lower alkyl esters of citric acid, such as triethyl citrate and tributyl citrate and the like, and aryl, aralkyl and lower alkyl ketones. Among preferred solvents are those having solubilities within the foregoing range selected from (i) compounds having the following structural formulas :

$$R_1 - \overset{\displaystyle O}{C} - O - R_2$$

polypropylene glycol dibenzoate, propylene glycol dibenzoate, diethylene glycol benzoate and dipropylene glycol benzoate blend, polyethylene glycol (200) dibenzoate, iso decyl benzoate, neopentyl glycol dibenzoate, glyceryl tribenzoate, pentaerylthritol tetrabenzoate, cumylphenyl benzoate, trimethyl pentanediol dibenzoate.

Art recognized phthalic acid derivatives from which solvents having the requisite solubility may be selected include: Alkyl benzyl phthalate, bis-cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diisobutyl phthalate, butyl octyl phthalate, diisoheptyl phthalate, butyl octyl phthalate, diisonoyl phthalate, nonyl undecyl phthalate, dioctyl phthalate, di-iso octyl phthalate, dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear heptyl, nonyl, phthalate, linear heptyl, nonyl, undecyl phthalate, linear nonyl phthalate, linear nonyl undecyl phthalate, linear dinoyl, didecyl phthalate (diisodecyl phthalate), diundecyl phthalate, ditridecyl phthalate, undecyldodecyl phthalate, decyltridecyl phthalate, blend (50/50) of dioctyl and didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

Preferred solvents include the lower alkyl and aralkyl esters of the aryl acids described above. Representative acids are benzoic acid and the phthalic acids, such as phthalic acid, isophthalic acid, and terephathalic acid. Most preferred solvents are derivatives of benzoic acid and include, but are not limited to, methyl benzoate, ethyl benzoate, n-propyl benzoate, isopropyl benzoate, butyl benzoate, isobutyl benzoate, *sec*-butyl benzoate, *tert*-butyl

Component solvents useful in component solvent mixtures are those solvents that are miscible with the primary solvent or solvent mixture, and include, but are not limited, to triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides, triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene, silicone fluid, glylcerin, ethylene glycol, polyethylene glycol, octanol, ethyl lactate, propylene glycol, propylene carbonate, ethylene carbonate, butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one, and mixtures thereof.

In an especially preferred embodiment, the primary solvent is selected from lower alkyl and aralkyl esters of benzoic acid and the polymer is a lactic-acid based polymer, most preferably PLGA, having a number average molecular weight of between about 8,000 to about 13,000, preferably about 10,000. Presently, the most preferred solvents are benzyl benzoate and the lower alkyl esters of benzoic acid. The benzoic acid esters may be used alone or in a mixture with other miscible solvents, e.g., triacetin, as described herein. Implants are prepared as viscous gels in which the beneficial agent is dissolved or dispersed substantially throughout, and such compositions are useful both for systemic and local administration of beneficial agent, whether or not initial burst is an important consideration. Additionally, use of esters of benzoic acid provides increased control of water migration resulting in

shown in Figure 4A, water uptake by a gel vehicle formed with the more water miscible solvent N-methyl-2-pyrrolidone (NMP) is higher than that for any other solvent-polymer combination, by about a factor of four or more. Water uptake for the combination of 80% benzyl benzoate and 20% NMP by weight in the solvent portion of the vehicle is less than a third that of NMP alone. Implants with benzyl benzoate take up the least water, whether compared to the other solvents alone or as mixtures with benzyl benzoate. Additionally, it can be seen that the 80/20 mixture of benzyl benzoate and triacetin takes up less than 10% water on a weight basis, and exhibits less water uptake than triacetin alone. Figure 4B provides a comparison of various solvents alone and demonstrates again the advantages of the benzoic acid esters, particularly that of benzyl benzoate. A relative comparison of the water uptake for the various solvents and the burst indices reproduced in the foregoing Table 1 show a correlation between low water uptake values and low burst indices. Gel compositions of this invention may take up 25 % or less of their bulk weight in water within the first 7 days, 30% in the first 14 days and 40% in the first 21 days, as tested in the water migration assay described herein.

hours after implantation may be reduced by one-third to two-thirds or more by the use of solubility modulators associated with the beneficial agent. Such modulators are typically coatings, substances that form complexes or otherwise associate with or stabilize the beneficial agent such as metallic ions, other stabilizing agents, waxes, lipids, oils, non-polar emulsions, and the like. Use of such solubility modulators may permit the use of more highly water soluble solvents or mixtures and achieve burst indices of 8 or less for systemic applications, or with respect to local applications, release of beneficial agent in the first 24 hours after implantation of not greater than 20% of the beneficial agent administered. Preferably that release will be not greater than 15% and more preferably not greater than 10%.

Limited water uptake by the compositions of this invention can often provide the opportunity to prepare compositions without solubility modulators when in other compositions such modulators would be necessary. For example with reference to Table 1, suitable burst indices are obtained for a composition of PLGA, benzyl benzoate and human growth hormone without the presence of Zn ion. Similar results may be obtained with other beneficial agents, such as the interferons, including interferon alpha-2a, interferon alpha-2b and consensus interferon.

In instances where the choice of solvent and polymer result in compositions severely restricting water uptake by themselves, it may be desirable to add osmotic agents or other agents and hydroattractants that facilitate water uptake to desired levels. Such agents may be, for example, sugars and the like, and are well known in the art.

beneficial agent, potential adverse consequences due to overdosing, cost of beneficial agent, and the type of effect desired, e.g., systemic or local. Preferably, 20% or less of the beneficial agent will be released in the first 24 hours after implantation, where the percentage is based on the total amount of beneficial agent to be delivered over the duration of the delivery period. Typically, higher percentages of release in the first 24 hours can be tolerated if the duration of the delivery period is relatively short, e.g., less than 7-14 days, or if the beneficial agent has a wide therapeutic window with little likelihood of side effects, or if the beneficial agent acts locally.

Depending on the particular solvent or solvent mixture selected, the polymer and beneficial agent, and optionally solubility modulators of the beneficial agent, the compositions of the present invention intended for systemic delivery may provide a gel composition having a burst index of 8 or less, preferably 6 or less, more preferably 4 or less and most preferably 2 or less. Compositions of PLGA with solvents having a miscibility in water of less than 7% by weight, optionally combined with the other solvents, providing implants intended for systemic delivery of beneficial agent having a burst index of 10 or less, preferably 7 or less, more preferably 5 or less and most preferably 3 or less, are particularly advantageous. The use of solvent mixtures as discussed herein can be particularly advantageous as a means of providing sufficient plasticizing of the polymer to obtain viscous gel formation and at the same time meet the desired burst indices and percentage release objectives of the compositions of the invention.

The solvent or solvent mixture is typically present in an amount of from about 95 to about 20% by weight and is preferably present in an amount of from about 70 to about 30% by weight and often 60-40% by weight of the viscous gel, i.e., the combined amounts of the polymer and the solvent. The viscous gel formed by mixing the polymer and the solvent typically exhibits a viscosity of from about 1,000 to about 200,000 poise, preferably from about 5,000 to about 50,000 poise measured at a 1.0 sec^{-1} shear rate and 25°C using a Haake Rheometer at about 1-2 days after mixing is completed. Mixing the polymer with the solvent can be achieved with conventional low shear equipment such as a Ross double planetary mixer for from about 10 minutes to about 1 hour, although shorter and longer periods may be chosen by one skilled in the art depending on the particular physical characteristics of the composition being prepared. Since it is often desirable to administer the implant as an injectable composition, a countervailing consideration when forming implants that are viscous gels is that the polymer/solvent/beneficial agent composition have sufficiently low viscosity in order to permit it to be forced through a small diameter, e.g., 18-20 gauge needle. If necessary, adjustment of viscosity of the gel for injection can be accomplished with emulsifying agents as described herein. Yet, such compositions should have adequate dimensional stability so as to remain localized and be able to be removed if necessary. The particular gel or gel-like compositions of the present invention satisfy such requirements.

If the polymer composition is to be administered as an injectable gel, the level of polymer dissolution will need to be balanced with the resulting gel

an average diameter of less than about 100 microns. The continuous phase is formed of the polymer and the solvent. The particles of the beneficial agent may be dissolved or dispersed in either the continuous phase or the droplet phase. In the resulting thixotropic composition, the droplets of emulsifying agent elongate in the direction of shear and substantially decrease the viscosity of the viscous gel formed from the polymer and the solvent. For instance, with a viscous gel having a viscosity of from about 5,000 to about 50,000 poise measured at 1.0 sec^{-1} at 25°C, one can obtain a reduction in viscosity to less than 100 poise when emulsified with a 10% ethanol/water solution at 25°C as determined by Haake Rheometer.

When used, the emulsifying agent typically is present in an amount ranging from about 5 to about 80%, preferably from about 20 to about 60% and often 30 to 50% by weight based on the amount of the injectable depot gel composition, that is the combined amounts of polymer, solvent, emulsifying agent and beneficial agent. Emulsifying agents include, for example, solvents that are not fully miscible with the polymer solvent or solvent mixture. Illustrative emulsifying agents are water, alcohols, polyols, esters, carboxylic acids, ketones, aldehydes and mixtures thereof. Preferred emulsifying agents are alcohols, propylene glycol, ethylene glycol, glycerol, water, and solutions and mixtures thereof. Especially preferred are water, ethanol, and isopropyl alcohol and solutions and mixtures thereof. The type of emulsifying agent affects the size of the dispersed droplets. For instance, ethanol will provide droplets that have average diameters that can be on the

tissue or bone. Such applications may permit loading of beneficial agent in the gel above concentrations typically present with injectable compositions.

The beneficial agent can be any physiologically or pharmacologically active substance or substances optionally in combination with pharmaceutically acceptable carriers and additional ingredients such as antioxidants, stabilizing agents, permeation enhancers, etc. that do not substantially adversely affect the advantageous results that can be attained by the present invention. The beneficial agent may be any of the agents which are known to be delivered to the body of a human or an animal and that are preferentially soluble in water rather than in the polymer-dissolving solvent. These agents include drug agents, medicaments, vitamins, nutrients, or the like. Included among the types of agents which meet this description are lower molecular weight compounds, proteins, peptides, genetic material, nutrients, vitamins, food supplements, sex sterilants, fertility inhibitors and fertility promoters.

Drug agents which may be delivered by the present invention include drugs which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system and the central nervous system. Suitable agents may be selected from, for example, proteins, enzymes, hormones, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins,

indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinolpril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further examples are proteins and peptides which include, but are not limited to, bone morphogenic proteins, insulin, colchicine, glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, somatostatin, lypressin, pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists, leuprolide, interferons such as interferon alpha-2a, interferon alpha-2b, and consensus interferon, interleukins, growth hormones such as human growth hormone and its derivatives such as methione-human growth hormone and des-phenylalanine human growth hormone, bovine growth hormone and porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility promoters, growth factors such as insulin-like growth factor, coagulation

those compounds that are clinically useful and effective but may have adverse side effects.

To the extent not mentioned above, the beneficial agents described in aforementioned U.S. Patent No. 5,242,910 can also be used. One particular advantage of the present invention is that materials, such as proteins, as exemplified by the enzyme lysozyme, and cDNA, and DNA incorporated into vectors both viral and nonviral, which are difficult to microencapsulate or process into microspheres can be incorporated into the compositions of the present invention without the level of degradation caused by exposure to high temperatures and denaturing solvents often present in other processing techniques.

The beneficial agent is preferably incorporated into the viscous gel formed from the polymer and the solvent in the form of particles typically having an average particle size of from about 0.1 to about 100 microns, preferably from about 1 to about 25 microns and often from 2 to 10 microns. For instance, particles having an average particle size of about 5 microns have been produced by spray drying or freeze drying an aqueous mixture containing 50% sucrose and 50% chicken lysozyme (on a dry weight basis) and mixtures of 10-20% hGH and 15-30 mM zinc acetate. Such particles have been used in certain of the examples illustrated in the figures. Conventional lyophilization processes can also be utilized to form particles of beneficial agents of varying sizes using appropriate freezing and drying cycles.

Release rates and loading of beneficial agent will be adjusted to provide for therapeutically-effective delivery of the beneficial agent over the intended sustained delivery period. Preferably, the beneficial agent will be present in the polymer gel at concentrations that are above the saturation concentration of beneficial agent in water to provide a drug reservoir from which the beneficial agent is dispensed. While the release rate of beneficial agent depends on the particular circumstances, such as the beneficial agent to be administered, release rates on the order of from about 0.1 to about 100 micrograms/day, preferably from about 1 to about 10 micrograms per day, for periods of from about 7 to about 90 days can be obtained. Greater amounts may be delivered if delivery is to occur over shorter periods. Generally, higher release rate is possible if a greater burst can be tolerated. In instances where the gel composition is surgically implanted, or used as a "leave behind" depot when surgery to treat the disease state or another condition is concurrently conducted, it is possible to provide higher doses that would normally be administered if the implant was injected. Further, the dose of beneficial agent may be controlled by adjusting the volume of the gel implanted or the injectable gel injected. As can be seen from Figure 2 with respect to lysozyme, with more highly viscous systems, one can avoid a burst effect and deliver on the order of 1% by weight of the beneficial agent in the composition during the first day.

Figures 5A and 5B illustrate representative release profiles of human growth hormone ("hGH") obtained in rats from preferred compositions of this invention. The benefits of benzyl benzoate are apparent in that comparison.

modulator or stabilizing agent to beneficial agent of about 100:1 to 1:1, preferably 10:1 to 1:1, typically can be utilized.

Pore forming agents include, biocompatible materials that when contacted with body fluids dissolve, disperse or degrade to create pores or channels in the polymer matrix. Typically, organic and non-organic materials that are water soluble such as sugars (e.g., sucrose, dextrose), water soluble salts (e.g., sodium chloride, sodium phosphate, potassium chloride, and sodium carbonate), water soluble solvents such as N-methyl-2-pyrrolidone and polyethylene glycol and water soluble polymers (e.g., carboxmethylcellulose, hydroxypropylcellulose, and the like) can conveniently be used as pore formers. Such materials may be present in amounts varying from about 0.1% to about 100% of the weight of the polymer, but will typically be less than 50% and more typically less than 10-20% of the weight of polymer.

Compositions of this invention without beneficial agent are useful for wound healing, bone repair and other structural support purposes.

To further understand the various aspects of the present invention, the results set forth in the previously described Figures were obtained in accordance with the following examples.

Example 1

Lysozyme particles were made by spray drying 50% sucrose and 50% chicken lysozyme (on a dry weight basis).

A viscous gel material was prepared by heating 60% by weight of triacetin with 40% by weight of a 50:50 lactic acid:glycolic acid copolymer to

hGH solution (5 mg/ml) solution in water (BresaGen Corporation, Adelaide, Australia) was concentrated to 10 mg/mL using a Concentration/ Dialysis Selector diafiltering apparatus. The diafiltered hGH solution was then washed with 5 times volume of tris or phosphate buffer solution (pH 7.6). Particles of hGH were then formed by spray drying or lyophilization using conventional techniques. Phosphate buffer solutions (5 or 50 mM) containing hGH (5 mg/mL) and various levels of zinc acetate (0 to 30 mM) were spray-dried using a Yamato Mini Spraydryer set at the following parameters:

Spray Dryer Parameter	Setting
Atomizing Air	2 psi
Inlet Temperature	120°C
Aspirator Dial	7.5
Solution Pump	2-4
Main Air Valve	40-45 psi

hGH particles having a size range between 2 - 100 microns were obtained. Lyophilized particles were prepared from tris buffer solutions (5 or 50 mM: pH 7.6) containing hGH (5 mg/mL) and various levels of zinc acetate (0 to 30 mM) using a Durastop μP Lyophilizer in accordance with the following freezing and drying cycles:

Freezing Cycle	Ramp down at 2.5 C/min to -30 C and hold for 30 minutes
	Ramp down at 2.5 C/min from -30 C to -50C and hold for 60 minutes
Drying Cycle	Ramp up at 0.5 C/min to 10 C and hold for 960 min
	Ramp up at 0.5 C/min to 20 C and hold for 480 min
	Ramp up at 0.5 C/min to 25 C and hold for 300 min
	Ramp up at 0.5 C/min to 30 C and hold for 300 min
	Ramp down at 0.5 C/min to 5 C and hold for 5000 min

hGH particles having a size range between 2 - 100 microns were obtained.

spatula, resulting in a sticky amber paste-like substance containing white polymer particles. The vessel containing the polymer/solvent mixture was sealed and placed in a temperature controlled incubator equilibrated to 39°C. The polymer/solvent mixture was removed from the incubator when it appeared to be a clear amber homogeneous gel. Incubation time intervals ranged from 1 to 4 days, depending on solvent and polymer type and solvent and polymer ratios. Additional depot gel vehicles are prepared with the following polymers: Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® L104, PLGA-L104, code no. 33007, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG206, PLGA-206, code no. 8815, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG502, PLGA-502, code 0000366, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG502H, PLGA-502H, code no. 260187, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG503, PLGA-503, code no. 0080765, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG506, PLGA-506, code no. 95051, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG755, PLGA-755, code no. 95037, (Boehringer Ingelheim Chemicals, Inc., Petersburg, VA), and the following solvents or mixtures: glyceryl triacetate (Eastman Chemical Co., Kingsport, TN), benzyl benzoate ("BB"), ethyl benzoate ("EB"), methyl benzoate ("MB"), triacetin ("TA"), and triethyl citrate ("TC") (Aldrich Chemical Co., St Louis, MO). When solvent combinations were used, for example 20% triacetin and 80% benzyl benzoate, the solvent mixture was directly added to the pre-weighed dry polymer. Typical polymer molecular weights were in the range of 14,400 - 39,700 (M_w) [6,400-12,200 (M_n)]. Representative gel vehicles are described in Table 2 below.

Table 3: In Vivo hGH

Formulation	Polymer		Solvent		Drug Particle			Trizma
	Level	PLGA	Level	Type	Level	Process	Zinc Level (mM)	Buffer (mM)
A	45%	502	45%	TA	10%	L	0	50
B	45%	502	45%	TA	10%	L	7.5	50
C	45%	502	45%	TA	10%	L	15	50
D	45%	502	45%	BB	10%	L	0	50
E	45%	502	45%	BB	10%	L	7.5	50
F	45%	502	45%	BB	10%	L	15	50
G	45%	502	45%	NMP	10%	L	0	50
H	45%	502	45%	NMP	10%	L	15	50
I	45%	502	45%	TA	10%	SD	0	50
J	45%	502	45%	TA	10%	SD	7.5	50
K	45%	502	45%	BB	10%	SD	0	50
L	45%	502	45%	BB	10%	SD	7.5	50

Table 4: In Vivo hGH (zinc level in all cases was 15 mM)

Formulation	Polymer		Solvent		Drug Particle		Trizma
	Level	PLGA	Level	Type	Level	Process	Buffer (mM)
F	45%	502	45%	BB	10%	L	50
N	45%	502	45%	80%BB/20%TA	10%	L	5
P	45%	502H	45%	TA	10%	L	5
Q	45%	502H	45%	BB	10%	L	5
R	45%	502	45%	EB	10%	L	5
S	45%	502	45%	TC	10%	L	5
T	40%	502	40%	BB	20%	L	5
W	45%	502-2	45%	BB	10%	L	5
X	45%	502	45%	TA	10%	L	5

Example 3 - Lysozyme In Vitro Studies

Lysozyme from chicken egg white (Sigma Chemical Co., St Louis, MO) in vitro release studies were used to test different vehicle formulations with the highly water soluble solvent NMP and the less soluble solvents triacetin and benzyl benzoate useful in the present invention. A depot gel formulation was dispensed from a 3 cc disposable syringe and weighed onto a Delrin™ cup platform or a 250 μ mesh 1 square inch polypropylene screen. Then, the cup or screen containing a depot gel formulation was immersed into a plastic

and final depot gel vehicle weights were recorded to observe weight change. Water content was obtained from depot gel vehicles using a Karl Fischer Apparatus, Mitsubishi Moisture Meter CA-06 equipped with Vaporizer VA-06. Results are illustrated in Figures 4A-4B for selected gels. Those results demonstrate that gel compositions of this invention take up substantially less water than gel compositions formed with NMP alone.

Example 5 - hGH In Vivo Studies

In vivo studies in rats were performed following an open protocol to determine serum levels of hGH upon systemic administration of hGH via the implant systems of this invention. Depot gel hGH formulations, spray-dried (SD) or lyophilized (L), were loaded into customized 0.5 cc disposable syringes. Disposable 16 gauge needles were attached to the syringes and were heated to 37°C using a circulator bath. Depot gel hGH formulations were injected into rats and blood was drawn at specified time intervals. All serum samples were stored at 4°C prior to analysis. Samples were analyzed for intact hGH content using a radio immuno assay (RIA). Representative results for triacetin and benzyl benzoate are illustrated in Figures 5A and 5B, and demonstrate the superior control of burst by the compositions of the present invention.

Example 6

Implant systems of this invention are prepared in accordance with Example 2 with equivalent quantities of interferon alpha-2a and -2b, consensus interferon, methionine human growth hormone, des-phenylalanine human growth hormone, carboplatin and insulin-like growth factor. The

burst effect and provide the desired beneficial agent release profile. Furthermore, once the beneficial agent has been fully administered, there is no need to remove the composition since it is fully biodegradable. As a still further advantage, the present invention avoids the use of microparticle or microencapsulation techniques which can degrade certain beneficial agents, like peptide and nucleic acid-based drugs and which microparticles and microcapsules may be difficult to remove from the environment of use. Since the viscous gel is formed without the need for water, temperature extremes, or other solvents, suspended particles of beneficial agent remain dry and in their original configuration, which contributes to the stability of thereof. Further, since a mass is formed, the injectable depot gel composition may be retrieved from the environment of use if desired.

The above-described exemplary embodiments are intended to be illustrative in all respects, rather than restrictive, of the present invention. Thus the present invention is capable of many variations in detailed implementation that can be derived from the description contained herein by a person skilled in the art. All such variations and modifications are considered to be within the scope and spirit of the present invention as defined by the following claims.

7. The method of Claim 5 wherein the polymer is a lactic acid-based polymer and the solvent is selected from lower alkyl and aralkyl esters of benzoic acid.

8. A method of locally administering a beneficial agent to a subject which comprises implanting a system comprising a beneficial agent dissolved or dispersed substantially throughout a viscous gel, the system releasing within 24 hours after implantation not greater than 20% by weight of the amount of beneficial agent to be delivered over the duration of the delivery period.

9. The method of Claim 8 wherein the viscous gel comprises a biocompatible polymer and a solvent.

10. The method of Claim 9 in which the viscous gel optionally includes one or more of the following: an emulsifying agent, a pore former, a solubility modulator for the beneficial agent, and an osmotic agent.

11. The method of Claim 10 wherein the solvent comprises a solvent having a miscibility in water of less than 7% by weight.

12. The method of Claim 11 wherein the solvent is selected from lower alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl ketones; and lower alkyl esters of citric acid.

13. The method of Claim 9 wherein the polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid),

comprises a single solvent or a mixture of solvents with at least one solvent having a miscibility in water of less than 7% by weight and the total amount of solvent constituting 40% or more by weight of the gel vehicle, said composition having a burst index of 8 or less.

19. An implantable, biodegradable composition for the sustained delivery of a beneficial agent to a subject wherein the composition comprises a polymer; an effective plasticizing amount of a solvent to form a viscous gel with the polymer; and a beneficial agent dissolved or dispersed in the gel, wherein the solvent comprises a mixture of solvents with at least one solvent in the mixture having a miscibility in water of less than 7% by weight.

20. The composition of Claim 19 wherein the miscibility in water of the solvent mixture is 10% or less by weight.

21. An implantable, biodegradable composition for delivery of a beneficial agent to a subject wherein the composition comprises a polymer; an effective plasticizing amount of a solvent to form a viscous gel with the polymer; and a beneficial agent dissolved or dispersed in the gel, wherein the solvent comprises a single solvent or a mixture of solvents with at least one solvent having a miscibility in water of less than 7% by weight selected from lower alkyl and aralkyl esters of benzoic acid.

22. An implantable gel composition for delivery of a beneficial agent to a subject comprising:

A) a biocompatible polymer;

C) a beneficial agent selected from the group consisting of cDNA, DNA, peptides, proteins and fragments and derivatives thereof, and optionally, one or more of the following:

D) an emulsifying agent;

E) a pore former;

F) a solubility modulator for the beneficial agent; and

G) an osmotic agent.

wherein the composition has a burst index of less than 8.

28. A kit for administration of a beneficial agent to a subject comprising:

A) a biocompatible polymer;

B) a solvent having a miscibility in water of 7% or less by weight that is suitable for dissolving the polymer and forming a viscous gel;

C) a beneficial agent; and optionally, one or more of the following:

D) an emulsifying agent;

E) a pore former;

F) a solubility modulator for the beneficial agent, optionally associated with the beneficial agent; and

G) an osmotic agent;

wherein at least the beneficial agent, optionally associated with the solubility modulator, is maintained separated from the solvent until the time of administration of the beneficial agent to a subject.

29. An implantable composition for the systemic delivery of a beneficial agent comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a

41. The composition of Claim 35 in which the emulsifying agent is selected from the group consisting of alcohols, propylene glycol, ethylene glycol, glycerol, water and solutions and mixtures thereof.

42. The composition of Claim 35 wherein the emulsifying agent is selected from the group consisting of ethanol, isopropyl alcohol, water, solutions thereof, and mixtures thereof.

43. The composition of Claim 30 wherein the copolymer has a monomer ratio of lactic acid to glycolic acid in the range of 100:0 to about 15:85.

44. The composition of Claim 30 wherein the copolymer has a number average molecular weight of from 1,000 to 120,000.

45. The composition of Claim 30 wherein the solvent comprises a component solvent miscible with the solvent.

46. The composition of Claim 45 wherein the component solvent is selected from the group consisting of triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides, triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene, silicone fluid, glylcerin, ethylene glycol, polyethylene glycol, octanol, ethyl lactate, propylene glycol, propylene carbonate, ethylene carbonate, butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one, and mixtures thereof.

59. The composition of Claim 18 wherein the gel remains non-rigid after implantation.

60. The composition of Claim 59 wherein the gel maintains a glass transition temperature below 37°C for at least 24 hours after implantation.

61. An implantable gel composition comprising a biocompatible polymer, a biocompatible solvent forming a viscous gel with the polymer, and a beneficial agent, the composition imbibing 40% or less of its bulk weight in water within the first 21 days after implantation.

62. The composition of Claim 61 wherein the composition imbibes less than 30% of its bulk weight in water within the first 14 days after implantation.

63. The composition of Claim 62 wherein the composition imbibes less than 25% of its bulk weight in water within the first 7 days after implantation.

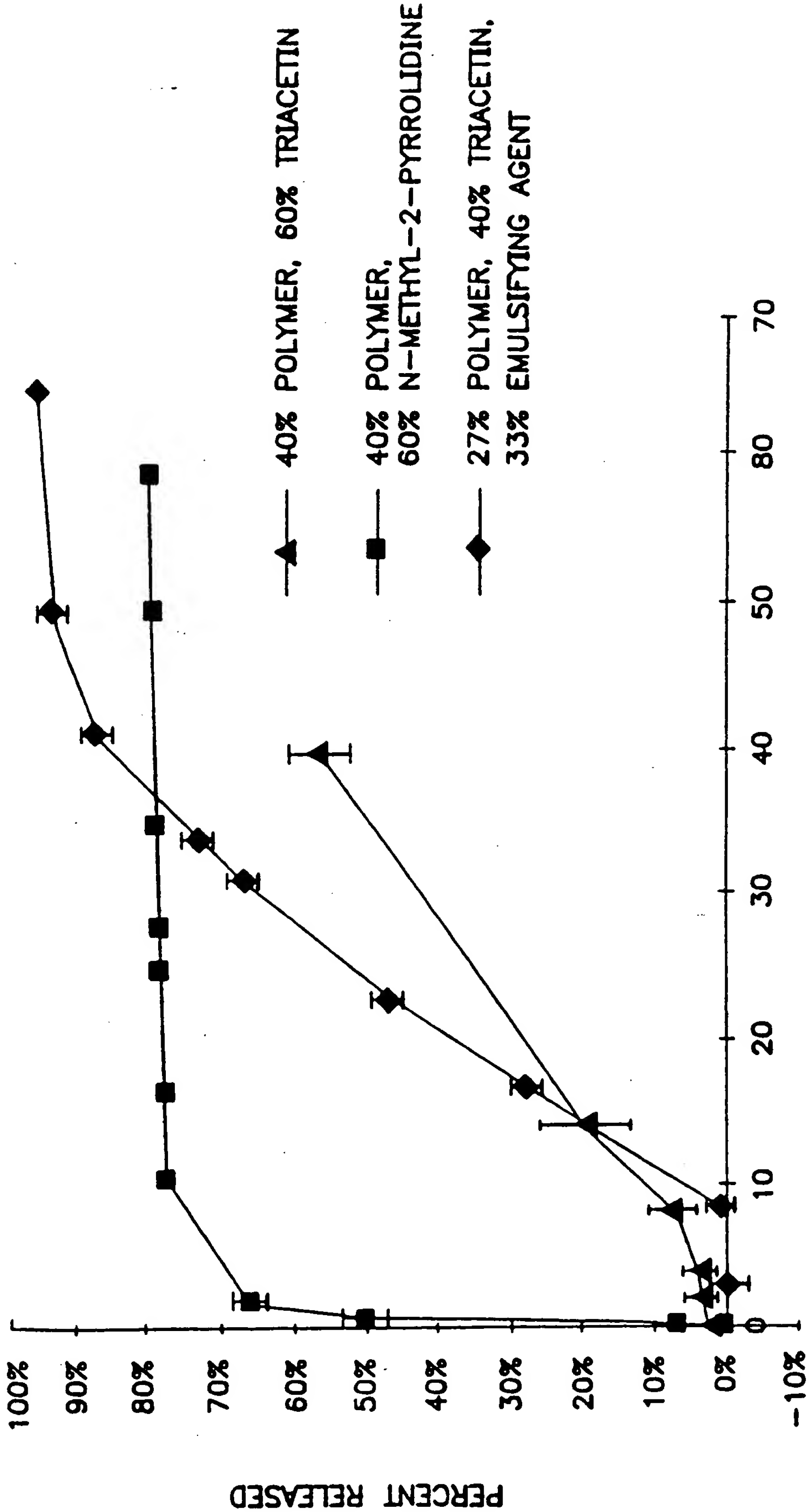
40% POLYMER, 60% TRIACETIN
40% POLYMER,
60% N-METHYL-2-PYRROLIDINE
27% POLYMER, 40% TRIACETIN,
33% EMULSIFYING AGENT
PERCENT RELEASED
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
-10%
TIME (DAYS)
0
10
20
30
40
50
60
70

FIG. 2

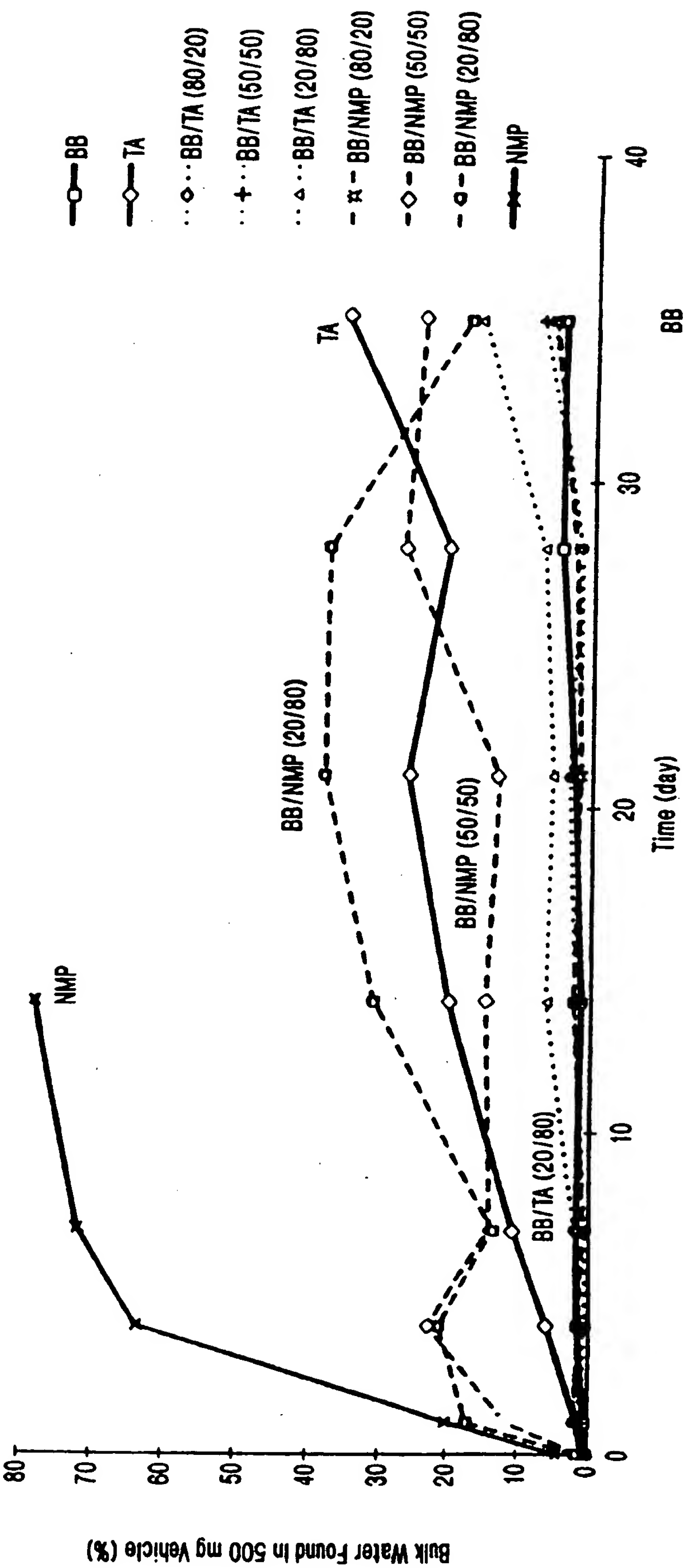
BB
TA
BB/TA (80/20)
BB/TA (50/50)
BB/TA (20/80)
BB/NMP (80/20)
BB/NMP (50/50)
BB/NMP (20/80)
NMP
BB/NMP (20/80)
BB/NMP (50/50)
BB/TA (20/80)
0
10
20
30
40
50
60
70
80
Bulk Water Found in 500 mg Vehicle (%)
Time (day)

FIG. 4A

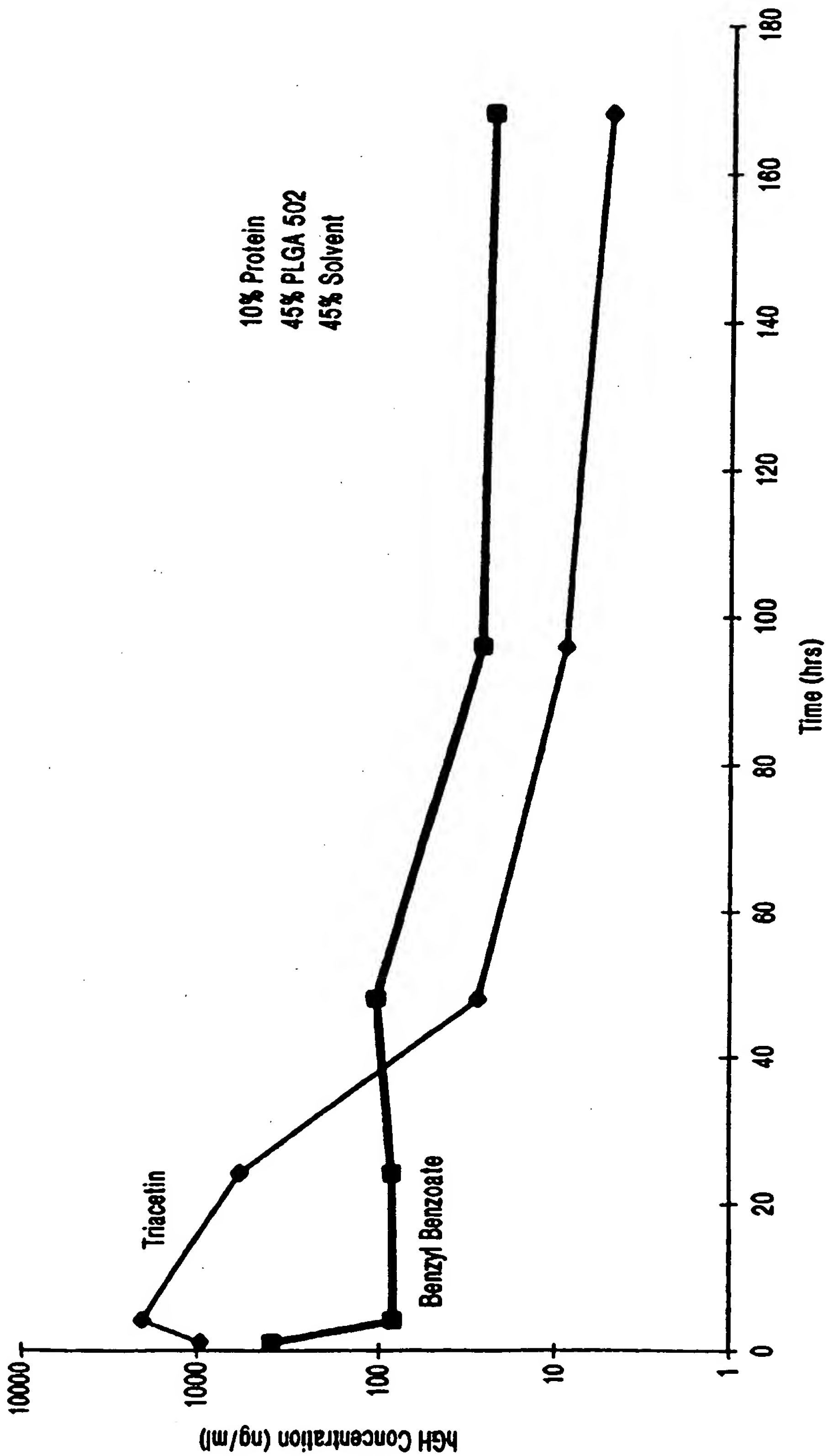
10% Protein
45% PLGA 502
45% Solvent
Triacetin
Benzyl Benzoate
hGH Concentration (ng/ml)
10000
1000
100
10
1
0
20
40
60
80
100
120
140
160
180
Time (hrs)

FIG. 5A